# Health Consultation

Sulfolane



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## Introduction and Background

The Alaska Department of Health and Social Services requested that the ATSDR Division of Toxicology and Environmental Medicine review the chemical specific health consultation for the chemical sulfolane issued in February 2010 (ATSDR 2010). Sulfolane has been detected in the groundwater under the city of North Pole, Alaska and a completed exposure pathway exists to residents through the groundwater. Alaska previously requested that ATSDR develop a public health action level for sulfolane in the drinking water, as well as describe potential health effects of sulfolane exposure. The public health action level is a non-regulatory level set to identify if human exposure needs to be evaluated further. ToxStrategies, a contractor for the site's potentially responsible party, provided additional toxicological studies of sulfolane, and expressed concerns about the methodology ATSDR employed in setting the action level for sulfolane (ToxStrategies 2010). ToxStrategies presented several alternative screening values, all derived with Benchmark Dose (BMD) methodology. In brief, BMD methods utilize non-linear curve fitting software to fit a dose-response curve to the toxicological testing data. A point of departure, usually the 10% response rate ($BMD_{10}$) for dichotomous data or the 1 standard deviation ($BMD_{1SD}$) change in a continuous variable, is established. The methodology then calculates a lower statistical confidence on this BMD, referred to as the lower confidence limit of the benchmark dose (BMDL). BMD methods are technically complex. Therefore, in light of these issues, Alaska specifically requested ATSDR to review:

1. Does the new information warrant revision to the ATSDR recommendations for the site action level?
2. Do the data support the use of child specific and infant specific consumption and body weights in the action level of sulfolane?
3. Which is the appropriate point of departure for setting a health guidance value dose for sulfolane?

### Summary of Previous Health Consultation

Sulfolane is an industrial solvent used in liquid-liquid and liquid-vapor extraction of compounds such as aromatic hydrocarbons from petroleum (Brown et al. 1966; Andersen 1976; HSDB 2006). Sulfolane has also been reportedly used in fractionalization of wood tars, a component of hydraulic fluid, textile finishing, and as a curing agent in epoxy resins (HSDB 2006). Sulfolane has reportedly no odor and is completely miscible in water, acetone, glycerol and many oils (Brown et al. 1966). Sulfolane mixes well in water, is not very volatile, not highly viscous and is highly polar.

Sulfolane is acutely toxic at relatively high doses (over 200 mg/kg) in several species tested (ATSDR 2010). While the acute toxicity of sulfolane has been characterized in a number of species, a paucity of data exists on the longer term effects of sulfolane (Table 1). Of the available sub-chronic studies, Zhu *et al*. 1987 was identified as the key study with effects noted in hepatic and lymphoreticular systems of rats (90 days) and guinea pigs (90 days and 6 months). An oral NOAEL for guinea pigs was identified as 0.25 mg/kg/day by the author of the study. In its February 2010 health consultation, ATSDR applied an uncertainty factor of 100 to the above

dose (10 for extrapolation from animals to humans, 10 to account for human variability), resulting in a health guidance value dose of 0.0025 mg/kg/day (2.5 µg/kg/day). Using standard water consumption assumptions (ATSDR 2005), this dose equates to the following action levels as protective of public health:

- 25 µg/l (ppb) for infant populations (Assumes 1 liter water per day at 10 kg bodyweight)
- 40 µg/l (ppb) for child populations (Assumes 1 liter water per day at 16 kg bodyweight)
- 87.5 µg/l (ppb) for adult populations (Assumes 2 liters water per day at 70 kg bodyweight)

## Discussion

An ad-hoc committee of ATSDR's Minimal Risk Level (MRL) workgroup was convened to review and discuss the February 2010 Health Consultation of sulfolane, and to review the information and issues raised by ToxStrategies in their August 2010 re-assessment of Sulfolane (Toxtrategies 2010). ToxStrategies presented a statistical analysis of 3 sub chronic studies[1] for the derivation of a health guidance value for sulfolane (Table 2). ToxStrategies utilized benchmark dose modeling for each of these data sets for the purpose of establishing a point of departure. We will briefly review each of the approaches and discuss their limitations.

### *ToxStrategies analysis of Zhu et al. 1987*

The data modeled for Zhu *et al*. 1987 are shown in Table 3. BMD models were fit to all health effects, with the fatty liver degeneration being the most sensitive health effect. ToxStrategies selected the log-logistic (restricted slope>1) model as the best "fit" the Zhu *et al.* fatty degeration liver data. A $BMD_{10}$ of 48.5 mg/kg/day, and a BMDL of 22.6 mg/kg/day was predicted by the slope restricted log-logistic model. A reproduction of the fitted curve is shown in Figure 1 (model output is in Appendix C). Zhu et al. 1987 was proposed by ToxStrategies in 2009 for establishing a health guidance level using the BMDL methodology (ToxStrategies 2009). A reference dose of 0.002 mg/kg/day was calculated according to Table 4. ToxStrategies used a dose scaling factor (based on the ratio of human to animal weight to the $1/4^{th}$ power) to scale the doses. Uncertainty factors were applied for animal to human extrapolation, human sensitivity, sub-chronic to chronic extrapolation and for database uncertainties.Based on a 2 liter per day intake and 70 kilogram body weight, ToxStrategies proposed a health guidance value of 730 ppb. ToxStrategies did not propose a child or infant specific screening levels, asserting that existing uncertainty factors are protective for children and infants.

As an alternative to benchmark dose approach, ToxStrategies discussed the use of one sided Fisher's Exact Test (FET) to test for statistical significance with Holm's correction for multiple comparisons. This statistical test revealed that the only dose that was statistically different from control for fatty degeneration of the liver was the 250 mg/kg/day (Table 5) (ToxStrategies 2010).

[1] ATSDR considers sub chronic exposure to be from 2 weeks to 1 year.

*Discussion of BMDL model of Zhu et al. 1987 data*

The ToxStrategies proposed log-logistic BMD curve, with the slope factor restricted to greater than 1, clearly underestimates the responses in the guinea pig. In the Zhu *et al.* study, at 2.5 mg/kg/day – 2/26 (8%) of guinea pigs had fatty degeneration of the liver. At 25 mg/kg/day, 4/25 (16%) guinea pigs had fatty degeneration of the liver. However, the slope restricted log-logistic regression of these data places the 10% response rate for the animals at 48.8 mg/kg/day, with a 95% lower confidence level of this dose at 22.6 mg/kg/day. These results are anticonservative in the 10 percent response rate of the dose response curve. In simulation, the BMD software that is used for log-logistic regression has been shown to be anticonservative in some cases, particularly when the slope is restricted (Kopylev and Fox, 2009). Consistent with EPA's guidance on benchmark dose modeling, ATSDR rejects the restricted model because it did not visually fit the data (EPA 2000).

*Discussion of Fishers Exact Test and Zhu et al. 1987 data.*

ATSDR has two criticisms regarding the statistical techniques used by ToxStrategies:

1. Fisher's Exact Test is noted to be highly conservative in that in it does not find significant difference (fails to rejects the null hypothesis) at the rate far less than what it nominally reported (Armitage, Berry and Matthews 2002). This is due to the discreteness of the probabilities calculated in FET.
2. An adjustment for multiple comparisons is not applicable due to the already statistically conservative nature of the techniques utilized and the strong evidence of dose-response trend in the data. Even after using the mid-p adjustment, the Fisher's Exact Test still does not meet the nominal alpha level (i.e., still conservative).

The conservative nature of the Fisher's Exact Test is well documented in the statistical research literature and recent articles advocate only using the Fisher's Exact Test with a mid-p adjustment (Armitage, Barry and Mathews 2002, Lydersen, Fagerland, Laake 2009). For a small sample where (n1,n2) = (20,20), Lin and Yang (2009) showed that the Fisher's Exact Test resulted in a p-value=0.0266 compared to the Fisher's Exact Test with the mid-p adjustment resulted in a p-value=0.0428 which was substantially closer to the nominal p-value=0.05 level. Using the Fisher's Exact Test with mid-p adjustment resulted in significance ($p<0.05$) at both 25 mg/kg/day and 250 mg/kg/day (Table 5).

***Alternative BMDL Approaches to Zhu et al. 1987 data***

Since ToxStrategies contacted the ATSDR assistant administrator expressing concerns about not using the BMD approach to sulfolane, ATSDR re-visited possible approaches for the Zhu *et al*.paper. As noted previously, the slope restricted log-logistic model did not provide a good fit to the dose-response data in the study and was anti-conservative in the response range of concern. An ideal regression model would:

- provide good statistical fit of the data,

- have a low residual in the area of interest,
- visually fit the data it was created from, especially in the 10% response region.

ToxStrategies ,when it performed BMD analysis of the Huntington Life Sciences data utilized the natural logarithm of the dose+1 as the independent variable (ln(dose+1)) (ToxStrategies 2010). The justification for this transformation was that the highest doses unduly influenced the model fit. A similar case exists in the Zhu *et al*. data and regression using the ln(dose+1) should be explored.

ATSDR considered all dichotomous models in the EPA Benchmark Dose Modeling Software, BMDS version 2.1.2 (EPA 2010). Tables 6 and 7 show the output of the BMDS for both the regression of dose vs. response and the regression of ln(dose+1) versus response. The best fitting (highest p-value and lowest Akaike Information Criterion (AIC)) was the quantal-linear model of the log(dose+1) values. It also is the most parsimonious of all models considered since, when the ln(dose+1) is inserted into the quantal-linear function, it reduces to:

$$p(dose) = \gamma + (1-\gamma)(1-(1+dose)^{-\beta})$$

Where γ is the background and β is the slope. Showing the function in its reduced form clearly shows that as dose approaches zero, the maximum slope of the dose response curve is limited by β, since the derivative of the above equation is:

$$p'(dose) = (1-\gamma)(\beta(1+dose)^{-\beta-1})$$

A $BMD_{10}$ of 4.58 mg/kg/day is calculated with this model, which is reasonably placed between doses of 2.5 mg/kg/day (8% response) and 25 mg/kg/day (16% response). A $BMDL_{10}$ of 2.07 mg/kg/day is also reasonably close to the 8% response rate found at 2.5 mg/kg/day. While the quantal-linear model results in a lower $BMD_{10}$ than the unrestricted log-logistic model, the quantal-linear model results in a higher BMDL than the unrestricted log-logistic model. The quantal-linear model resulted in a strong and statistically significant regression ($p>0.95$) of the data. A visual presentation of the regressions of the two models is shown in Figure 2. The output of the modeling for the log-logistic and the quantal-linear BMD model using EPA's Benchmark Dose Software is shown in Appendix C.

### *ATSDR Derivation of Provisional Health Guidance Value using Zhu et al. 1987*

The utilization of the BMD methodology outlined above would not substantially alter ATSDR's recommended dose or public health action levels. A review by the ATSDR Minimal Risk Level workgroup recommended that the NOAEL for the Zhu *et al*. be set at 2.5 mg/kg/day and a minimal LOAEL of 25 mg/kg/day. The MRL workgroup committee also recommended a total uncertainty factor of 1000 (10 for animal to human extrapolation, 10 for variability in human sensitivity, and 10 for extrapolation of a sub-chronic dose to a chronic dose). While an uncertainty factor 1000 is higher than the original uncertainty factor 100, it is in line with the total uncertainty proposed by ToxStrategies (300 times a dose scaling factor of 3.44). Both the ATSDR BMD approach and the NOAEL/UF approach results in essentially the same dose level (Table 8), although ATSDR does not use dose scaling to account for animal to human

uncertainty in derivation of health guidance values. ATSDR's conclusion is that a proper fitting BMD model would only marginally decrease the recommended dose level and subsequent public health action levels by 12%. Such a small difference does not warrant an adjustment downward without further evidence that sulfolane presents a greater toxicity hazard than has been reported in the literature.

***Huntington Life Sciences 2001***

Huntington Life Sciences (HLS) (2001), conducted a detailed 90-day study of male and female rats exposed to sulfolane in their drinking water *ad libitum*. Only 10 rats per sex per dose group were exposed. At the time of the ATSDR's original health consultation, this study was unavailable to the agency for review, although summaries of it existed (CCME 2006). ToxStrategies obtained a copy of this study and have provided it to ATSDR. A comprehensive battery of observations (weight, food/water intake, reflexes, and behavior) and examination of 13 major organ systems (adrenals, brain, femur, heart, ileum, kidneys, liver, lungs, mammary area, spinal cord, stomach, thyroid, and uterus) was conducted. The only significant effect to human health that was reported was a reduction of white blood cell and lymphocyte counts in female rats (NOAEL=2.9 mg/kg/day). The HLS study increases the available data for consideration in development of a health based guidance value. However, the rats in the HLS study did not suffer from fatty degeneration of the liver nor effects on the spleen, even at doses as high as 191 mg/kg/day, suggesting that the rat is not the most sensitive species in sub-chronic and chronic health end points.

In the absence of adequate human data, ATSDR will normally select the most sensitive animals and endpoints for derivation of health guidance values. Nevertheless, others have recommended using the Huntington Life Sciences study for derivation of the health guidance values. The Canadian Council of Ministers of the Environment calculated a tolerable daily intake for sulfolane based on the Huntington Life Sciences NOAEL of 2.9 mg/kg/day in female rats (CCME 2006). Uncertainty factors of 10 for human to animal extrapolation, 10 for human variability, and 3 for extrapolation to chronic exposures as well as other database uncertainties were used. A total uncertainty factor of 300 was applied for a tolerable daily intake of 0.0097 mg/kg/day (9.7 µg/kg/day) Using default Canadian drinking water guidance, CCME derive a drinking water guidance value of 0.09 mg/l (90 µg/l or ppb) for adult receptors drinking 1.5 liters of water a day.

ToxStrategies utilized benchmark dose modeling to fit a linear model of the ln(dose+1) to the WBC and lymphocyte data and modeling a benchmark response dose representing 1 standard deviation reduction in laboratory historical white blood cell counts in the female rats (ToxStrategies 2010). Three model regressions (Linear, Exponential M2, Exponential M4) fitted to the data with almost identical p-values, and virtually identical Akaike's Information Criterion (AIC), with BMDL of 15.12, 8.30, and 4.93 mg/kg/day, respectively). On the basis of "parsimony", ToxStrategies selected the linear regression of the ln (1+dose). This dose was approximately seven times higher than ATSDR's point of departure using the Zhu *et al*. guinea pig data.

Had ATSDR selected HLS 2001 as its key study, a BMDL of 4.93 mg/kg/day would have been selected as ATSDR will select the lowest BMDL when the differences in the model predictions are more than three-fold (see ATSDR 2009). Neither of the HLS 2001 BMD regressions is more

parsimonious than the other. Algebraic reduction of the linear model results in an equation with a logarithm function:

$$Y[dose] = beta_0 + beta_1 * (\ln(1 + dose))$$

and the exponential (M2) model reduces to:

$$Y[dose] = a \times (dose + 1)^{-b}$$

Both models are equally complex in terms of functions and number of variables. In considering the exponential equation, exponential submodel M2 and M4 resulted in the identical curves. The difference in BMDL is a result of submodel M4 having an additional parameter which improved the likelihood in the regressions of the $BMDL_{1SD}$ . This resulted in a BMDL for submodel M2 of 8.3 mg/kg/day as compared to submodel M4 (4.93 mg/kg/day).

***Japanese Ministry of Health 1999***

A reproduction/developmental toxicity screening test was reported in an Organization for Economic Cooperation (OECD) report (OECD 2004). This study was conducted by Japanese Ministry of Health (MHW 1999) and the report was peer reviewed by OECD. Rats were dosed at 0, 60, 200, or 700 mg/kg/d by gavage for 41 to 50 days from 14 days prior to mating to day 3 of lactation. Some mortality occurred in the high-dose group. There was a decrease in body weight gain and food consumption for males and females during the pre-mating period at 700 mg/kg/day. The number of oestrus cycles was decreased in the 700 mg/kg/day group. Four dams lost all their pups during the lactation period in the 700 mg/kg/day group. Birth index, live index, number of pups on days 1 and 4 of lactation, viability index and body weights of pups of both sexes on days 0 and 4 of lactation decreased, and the number of still births increased in the 700 mg/kg/day group. Delivery and birth index were decreased in the 200 mg/kg/d group. The NOAEL for reproductive and developmental toxicity was 60 mg/kg/day. There were no treatment-related findings in the external appearance, general conditions and necropsy findings in offspring at 60 mg/kg/day.

ToxStrategies used BMDS to fit $BMDL_{1SD}$ models to both the birth index and the number of live pups. $BMDL_{1SD}$.for the live pups on day 4 ranged from 96-161 mg/kg/day and for birth index, a single model fit at 120 mg/kg/day. As discussed in ATSDR's original health consultation, developmental effects occur at relatively high doses (1/2 the lethal dose 50%) and probably are not relevant for risk assessment purposes. Therefore, BMDL modeling of these data, while useful for answering concerns from the community, are not useful in developing a provisional health guidance value.

***Child-Specific Intake Factors***

ATSDR's use of child specific intake factors for health guidance values are outlined in the Public Health Assessment Guidance Manual (ATSDR 2005) and is established policy. The ATSDR Action Levels are set with goal of being health protective; they represent only the beginning of the health assessment process if values are exceeded. Exceeding a recommended action levels supports the need for a detailed public health toxicological assessment. As such, if

site-specific or chemical-specific information warrants a different calculation of intake factors or body weights or risk these can be examined during the detailed toxicological assessment.

## Conclusions

1. ATSDR selected the Zhu *et al*. 1987 as the key study because it represents the longest period studied in the most sensitive animal end point.

2. The MRL workgroup analyzed the Zhu *et al*. 1987 data, and found the appropriate minimal LOAEL to be 25 mg/kg/day based on a statistically significant ($p<0.05$) result in the liver data. Consistent with MRL workgroup practices of choosing the highest NOAEL, 2.5 mg/kg/day is recommended as a point of departure for establishing a provisional health guidance value. The Zhu *et al.* data were not amenable to benchmark models proposed by ToxStrategies, but an alternate BMDL model found a similar (but slightly lower) point of departure as the proposed ATSDR NOAEL point of departure. Therefore the NOAEL/LOAEL approach is appropriate in this case.

3. An additional uncertainty factor of 10 should be applied in extrapolating from sub chronic to chronic exposure (ATSDR considers chronic exposure to be greater than 1 year of exposure), resulting in a total uncertainty factor of 1000. This results in the same action level as previously published.

4. It is important to recognize the public health action level is specifically designed to support screening of environmental data using the process outlined in the ATSDR Public Health Guidance Manual (PHAGM) (ATSDR 2005). Simply put, they are set with goal of being health protective; they represent only the beginning of the health assessment process if values are exceeded. Exceeding the recommended action levels supports the need for a detailed public health toxicological assessment. A full public health assessment of levels exceeding the action level should include:

- Evaluating the experimental or human study(ies) on which the exceeded health guideline value was based. (Section 8.3 of the PHAGM).
- Determining where site-specific dose estimates fall in relation to other dose-response data. (Section 8.4 of the PHAGM).
- Reviewing other substance-specific factors that could increase or decrease the potential for harmful effects, such as our understanding of the overall behavior of the substance within the human body and the mechanism by which it exerts its toxic effect, knowledge of substance-specific effects among susceptible populations, and multiple chemical exposures. (Section 8.5 of the PHAGM).
- Determining whether relevant site-specific health effects data should be evaluated in the public health assessment, such as mortality and morbidity data (also called health outcome data), or biologic monitoring data (Section 8.6 of the PHAGM).

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# Appendix A – Tables

**Table 1: Sub- Chronic Studies of Sulfolane**

| Species | Effect | Route | Value | Source |
|---|---|---|---|---|
| **Rat** | NOAEL* – Respiratory | Inhalation<br>23 hrs/day 5 days/week<br>90 days | 20 mg/m$^3$ | (Andersen et al. 1977) |
| | LOAEL† – Inflamed hemorrhagic lungs | Inhalation<br>23 hrs/day 5 days/week<br>90 days | 159 mg/m$^3$ | (Andersen et al. 1977) |
| | LOAEL – Chronic inflammation | Inhalation<br>8 hrs/day 5 days/week<br>27 days | 495 mg/m$^3$ | (Andersen et al. 1977) |
| | NOAEL | Oral, 90 days | 167 mg/kg/day | (Zhu et al. 1987) |
| | LOAEL – Decreased ascorbic acid in adrenal glands | Oral, 90 days | 500 mg/kg/day | (Zhu et al. 1987) |
| | LOAEL – decreased birth index and number of pups (day 0 and 4 of lactation) | Oral<br>49 days (males)<br>41-50 days (females) | 200 mg/kg/day | (JMH 1999/OECD 2004) |
| | NOAEL – Reproductive<br>Developmental | Oral<br>49 days (males)<br>41-50 days (females) | 60 mg/kg/day | (JMH 1999/OECD 2004) |
| **Monkey** | LOAEL – Death | Inhalation<br>8 hrs/day 5 days/week<br>27 days | 495 mg/m$^3$ | (Andersen et al. 1977) |
| **Dog** | NOAEL – Respiratory | Inhalation<br>23 hrs/day 5 days/week<br>90 DAYS | 20 mg/m$^3$ | (Andersen et al. 1977) |
| | LOAEL – Inflamed hemorrhagic lungs | Inhalation<br>23 hrs/day 5 days/week<br>90 DAYS | 159 mg/m$^3$ | (Andersen et al. 1977) |
| **Guinea Pig** | LOAEL - Hepatic Effects Changes in Serum ALP<br>Changes in White Blood Cell count | Oral (6 months) | 2.5 mg/kg/day | (Zhu et al. 1987) |
| | NOAEL | Oral (6 months) | 0.25 mg/kg/day | (Zhu et al. 1987) |

*NOAEL: No Observed Adverse Effect Level

†LOAEL: No Observed Adverse Effect Level

**Table 2 – Studies considered in ToxStrategies (2010) for proposed Health Guidance Value**

| *Study* | *Animal* | *Period of Study* | *Doses (mg/kg/day)* | *Route* | *Critical Effects* |
|---|---|---|---|---|---|
| **Zhu *et al*. 1987** | Guinea Pig | 6 months | 0,0.25,2.5,25,250 | Oral | Fatty degeneration of the liver, Dispersion of the white pulp of the spleen, , reported changes in AST and ALT |
| **Huntington Life Sciences 2001** | Rat | 90 days | 0, 2.9, 10.6, 191.1 | Oral (drinking water) | White blood cell counts decreased, Lymphocytes decreased |
| **JMH 1999/OECD 2004** | Rat | 49 days (males)<br>41-50 days (females) | 60, 200, 700 mg/kg/day | Oral (gavage) | Birth index, decreased number of pups alive at day 0 and day 4 |

**Table 3 – Zhu *et al*. 6 month toxicity data (Guinea Pig)**

| *Oral Dose (mg/kg/day)* | *Spleen* | *Fatty Liver* | *Severe Fatty Liver* | *Bone Marrow Count* |
|---|---|---|---|---|
| **0** | 0/25 | 0/25 | 0/25 | $16.43 \times 10^4/mm^3$ |
| **0.25** | 0/22 | 0/22 | 0/22 | n.d. |
| **2.5** | 2/26 | 2/26 | 1/26 | $10.99 \times 10^4/mm^3$ |
| **25** | 2/25 | 4/25 | 2/25 | $12.25 \times 10^4/mm^3$ |
| **250** | 7/22 | 7/22 | 5/22 | $10.56 \times 10^4/mm^3$ |

**Table 4 – ToxStrategies RfD for Zhu *et al*. 1987 Fatty Liver Degeneration**

| *Point of Departure (mg/kg/day)* | *Dose Scaling Factor* | *Human Equivalent Dose (mg/kg/day)* | *Uncertainty Factors* | | | | | *RfD dose* |
|---|---|---|---|---|---|---|---|---|
| | | | **A** | **H** | **S** | **D** | **Total** | |
| 22.6 | 3.44 | 6.6 | 3 | 10 | | | 300 | 0.022 (0.02)* |

A: Animal to human extrapolation
H: Human variability uncertainty factor
S: Extrapolation from sub-chronic to chronic exposure
D: Database uncertainties
* Value rounded to 1 significant figure

**Table 5 – Analysis of Zhu *et al*. 1987 (Fatty Liver Degeneration) using Fisher's Exact Test**

| *Dose (mg/kg/day)* | *Number Animals with Fatty Liver Degeneration* | *Number of Animals* | *FET p-value (dose versus control)* | *FET mid-p value (dose versus control)* |
|---|---|---|---|---|
| Control | 0 | 25 | 1 | 1 |
| 0.25 | 0 | 22 | 1 | 1 |
| 2.5 | 2 | 26 | 0.255 | 0.127 |
| 25 | 4 | 25 | 0.0549 | 0.0275* |
| 250 | 7 | 22 | 0.00271* | 0.0014* |

* $p<0.05$

**Table 6 - BMDS Model Predictions for Fatty Liver in Guinea Pigs Exposed to Sulfolane for 6 Months using Dose as Independent Variable**

| Model Name | $X^2$ Goodness of fit p-value * | Akaike's Information Criterion | $BMD_{10}$ † (mg/kg/day) | $BMDL_{10}$ ‡ (mg/kg/day) |
|---|---|---|---|---|
| Gamma§ | 0.1479 | 74.0013 | 62.7786 | 34.8413 |
| Logistic | 0.0954 | 75.6726 | 129.605 | 93.4694 |
| LogLogistic | 0.8707 | 68.7461 | 9.45191 | 1.20719 |
| LogLogistic** | 0.1723 | 73.4695 | 48.5074 | 22.6332 |
| LogProbit | 0.0623 | 76.51 | 123.025 | 72.6384 |
| Multistage†† | 0.1479 | 74.0013 | 62.7785 | 34.8413 |
| Probit | 0.1 | 75.5307 | 120.472 | 85.2439 |
| Weibull§ | 0.1479 | 74.0013 | 62.7785 | 34.8413 |
| Quantal-Linear | 0.1479 | 74.0013 | 62.7785 | 34.8413 |

* Values <0.1 fail to meet conventional goodness-of-fit criteria
† $BMD_{10}$: Benchmark Dose (10% extra-risk)
‡ $BMDL_{10}$: Lower 95th confidence limit on $BMD_{10}$
§ Power restricted to ≥1
** Slope restricted to ≥1
†† Beta restricted to ≥0; 2-degree polynomial

**Table 7 - BMDS Model Predictions for Fatty Liver Degeneration in Guinea Pigs Exposed to Sulfolane for 6 Months using Naturally Logarithm of Dose+1 as Independent Variable**

| Model Name | $X^2$ Goodness of fit p-value * | Akaike's Information Criterion | $BMD_{10(ln(dose+1))}$ † (mg/kg/day) | $BMDL_{10(ln(dose+1))}$ ‡ (mg/kg/day) | $BMD_{10}$ † (mg/kg/day) | $BMDL_{10}$ ‡ (mg/kg/day) |
|---|---|---|---|---|---|---|
| Gamma§ | 0.9443 | 68.1163 | 1.97002 | 1.14629 | 6.17082 | 2.146498 |
| Logistic | 0.5361 | 70.6917 | 3.15222 | 2.47218 | 22.38793 | 10.84825 |
| LogLogistic | 0.8707 | 68.7461 | 1.94159 | 1.03608 | 5.969824 | 1.818148 |
| LogLogistic** | 0.9433 | 68.116 | 1.94159 | 0.850354 | 5.969824 | 1.340475 |
| LogProbit | 0.7519 | 67.0904 | 2.20054 | 1.64095 | 8.029888 | 4.160069 |
| Multistage†† | 0.9434 | 68.2002 | 2.00239 | 1.13891 | 6.406737 | 2.123362 |
| Probit | 0.5889 | 70.2067 | 2.94763 | 2.29141 | 18.06073 | 8.888871 |
| Weibull§ | 0.9443 | 68.1281 | 1.97954 | 1.14523 | 6.239412 | 2.143164 |
| **Quantal-Linear** | **0.9751** | **66.3896** | **1.7187** | **1.12291** | **4.577273** | **2.073786** |

*** Values <0.1 fail to meet conventional goodness-of-fit criteria**
**† $BMD_{10}$: Benchmark Dose (10% extra-risk)**
**‡ $BMDL_{10}$: Lower 95th confidence limit on $BMD_{10}$**
**§ Power restricted to ≥1**
**** Slope restricted to ≥1**
**†† Beta restricted to ≥0; 2-degree polynomial**

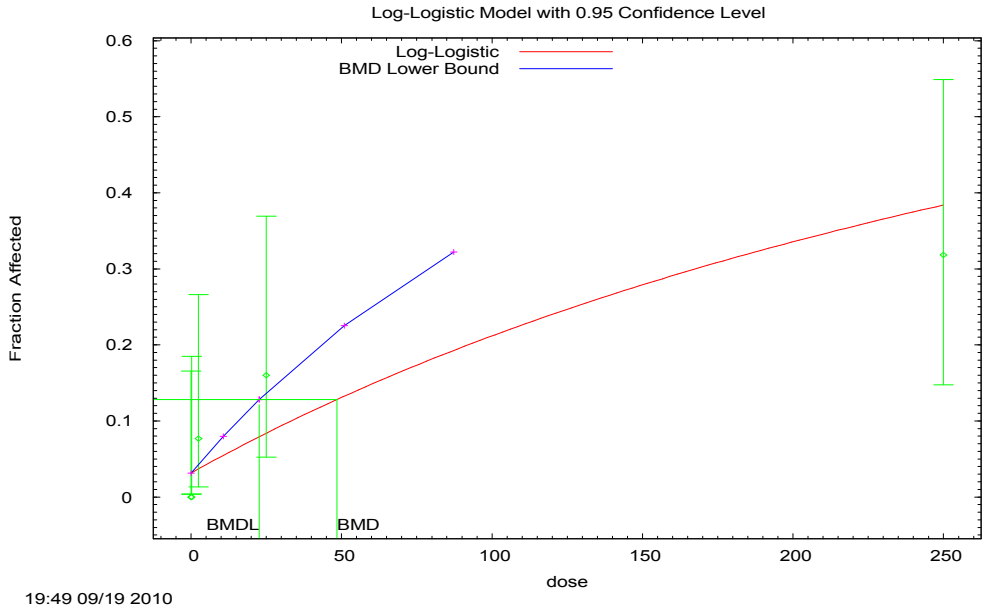
**Table 8 – ATSDR Health Guidance Level (HGV) for Sulfolane based on Zhu et al. 1987**

| *Source* | *Point of Departure (mg/kg/day)* | *Uncertainty Factors* | | | | | *p-HGV (dose)* |
|---|---|---|---|---|---|---|---|
| | | **A** | **H** | **S** | **D** | **Total** | |
| NOAEL/UF | 2.5 | 10 | 10 | 10 | | 1000 | 0.0025 |
| Quantile-linear BMD | 2.07 | 10 | 10 | 10 | | 1000 | 0.002* |

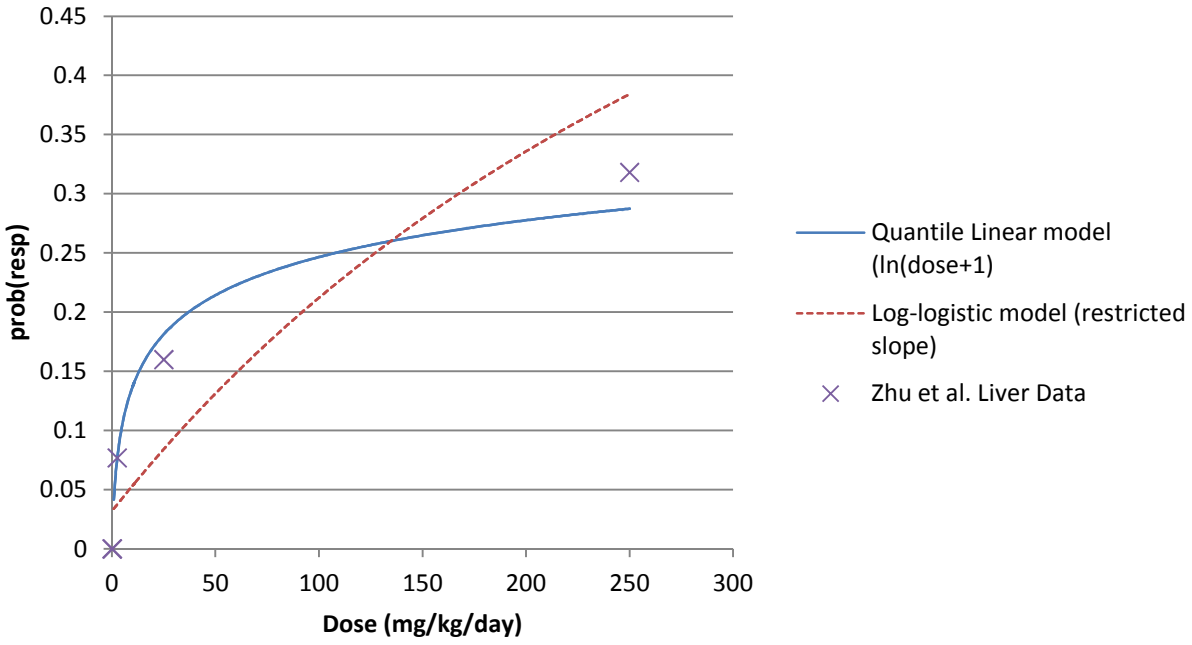
A: Animal to human extrapolation
H: Human variability uncertainty factor
S: Extrapolation from sub-chronic to chronic exposure
D: Database uncertainties
* Value rounded to 1 significant figure

# Appendix B – Figures

## Figure 1- Log Logistic Model Curve of Zhu et al. 1987.




## Figure 2- ATSDR BMD Models of Zhu et al. 1987.



# Appendix C – BMDS Output

## BMDS Output Quantal -Linear Model of Zhu 2007 Liver Data

```
 ================================================================
         Quantal Linear Model using Weibull Model (Version: 2.12;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Data\qln_lZhu_Liver_qlinear.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Data\qln_lZhu_Liver_qlinear.plt
                                                Fri Oct 01 15:48:42 2010
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-slope*dose)]


   Dependent variable = Observed
   Independent variable = lndose

   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial (and Specified) Parameter Values
                     Background =    0.0192308
                          Slope =    0.0679105
                          Power =            1   Specified


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Power
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                  Slope

     Slope            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background                0              NA
          Slope        0.0613026       0.0170554           0.0278747           0.0947305

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


                         Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -31.8035         5
```

| | | | | | |
|---|---|---|---|---|---|
| Fitted model | -32.1948 | 1 | 0.782644 | 4 | 0.9408 |
| Reduced model | -41.162 | 1 | 18.717 | 4 | 0.0008932 |

AIC: 66.3896

Goodness of Fit

| Dose | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---|---|---|---|---|---|
| 0.0000 | 0.0000 | 0.000 | 0.000 | 25 | 0.000 |
| 0.2231 | 0.0136 | 0.299 | 0.000 | 22 | -0.550 |
| 1.2528 | 0.0739 | 1.922 | 2.000 | 26 | 0.058 |
| 3.2581 | 0.1810 | 4.526 | 4.000 | 25 | -0.273 |
| 5.5255 | 0.2873 | 6.321 | 7.000 | 22 | 0.320 |

Chi^2 = 0.48 d.f. = 4 P-value = 0.9751

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1.7187

BMDL = 1.12291

## BMDS Output Log-Logistic Model of Zhu 2007 Liver Data (restricted slope)

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Data\lnl_lZhu_Liver_zhu_rest.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Data\lnl_lZhu_Liver_zhu_rest.plt
                                                Fri Oct 01 15:48:42 2010
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Observed
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =            0
                     intercept =     -5.81209
                         slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

             background    intercept

background            1        -0.47

 intercept        -0.47            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
    background        0.0314502            *               *                   *
     intercept         -6.07894            *               *                   *
         slope                1            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -31.8035         5
```

| | | | | | |
|---|---|---|---|---|---|
| Fitted model | -34.7347 | 2 | 5.86251 | 3 | 0.1185 |
| Reduced model | -41.162 | 1 | 18.717 | 4 | 0.0008932 |

AIC: 73.4695

Goodness of Fit

| Dose | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---|---|---|---|---|---|
| 0.0000 | 0.0315 | 0.786 | 0.000 | 25 | -0.901 |
| 0.2500 | 0.0320 | 0.704 | 0.000 | 22 | -0.853 |
| 2.5000 | 0.0370 | 0.961 | 2.000 | 26 | 1.080 |
| 25.0000 | 0.0839 | 2.098 | 4.000 | 25 | 1.372 |
| 250.0000 | 0.3841 | 8.451 | 7.000 | 22 | -0.636 |

Chi^2 = 4.99 d.f. = 3 P-value = 0.1723

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 48.5074

BMDL = 22.6332

## BMDS Output Log-Logistic Model of Zhu 2007 Liver Data (unrestricted slope)

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Data\lnl_lZhu_Liver_Lnl-BMR10-URestrict.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Data\lnl_lZhu_Liver_Lnl-BMR10-URestrict.plt
                                                 Fri Oct 01 15:48:41 2010
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Observed
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =            0
                     intercept =     -3.07235
                         slope =     0.432568


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -background
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

              intercept        slope

 intercept            1        -0.89

     slope        -0.89            1



                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background                0            *               *                   *
      intercept         -3.23397            *               *                   *
          slope         0.461552            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -31.8035         5
```

| | | | | | |
|---|---|---|---|---|---|
| Fitted model | -32.3731 | 2 | 1.13917 | 3 | 0.7676 |
| Reduced model | -41.162 | 1 | 18.717 | 4 | 0.0008932 |

AIC: 68.7461

Goodness of Fit

| Dose | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---|---|---|---|---|---|
| 0.0000 | 0.0000 | 0.000 | 0.000 | 25 | 0.000 |
| 0.2500 | 0.0204 | 0.448 | 0.000 | 22 | -0.676 |
| 2.5000 | 0.0567 | 1.475 | 2.000 | 26 | 0.445 |
| 25.0000 | 0.1483 | 3.707 | 4.000 | 25 | 0.165 |
| 250.0000 | 0.3350 | 7.371 | 7.000 | 22 | -0.167 |

Chi^2 = 0.71 d.f. = 3 P-value = 0.8707

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 9.45191

BMDL = 1.20719